Highly efficient synthesis of trans-β,γ-unsaturated-α-keto amides

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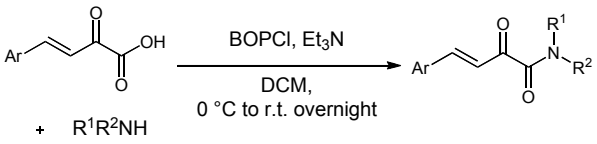
Abstract: A highly efficient, metal-free, and selective access to *trans*-β,γ-unsaturated-α-keto amides is described *via* peptidic coupling, involving easy to prepare *trans*-β,γ-unsaturated-α-keto acids and commercially available amines.

Key words: β,γ-unsaturated-α-keto amide; α-keto acid; amine; peptidic coupling; Michael acceptor.

α-Keto amides are compounds of widespread interest in organic chemistry since the electrophilicity of the ketone functionality is enhanced by the presence of electron-withdrawing group on the α-position. Apart from its enhanced reactivity, this functionality is also associated with biological properties[1], and α-keto amides are present in several bioactive natural products.[2] Therefore, development of numerous efficient synthetic strategies for their preparation emerged in the literature, particularly: 1) Ugi or Passerini like reactions from isonitriles;[3] 2) oxidation of amides,[4] α-hydroxyamides,[5] ynamides,[6] or N-glycosyl indoles;[7] 3) substitution on oxalyl chlorides;[8] 4) ring opening of cyclic dehydrodipeptides[9] or *N*-acetylisatins;[10] 5) oxidative cleavage of cyanoketo phosphoranes[11] or acyl derivatives of cyanomethylamines;[12] 6) peptidic coupling reactions;[13] 7) double carbonylation of aryl halides with amines;[14] 8) reactions of acyl chlorides with metallated carbamoyls.[15] However, none of these synthetic pathways are efficient for the preparation of β,γ-unsaturated-α-keto amides. Quite surprisingly, although β,γ-unsaturated-α-keto esters[16] or β,γ-unsaturated-α-keto phosphonates[17] are well documented,[18,19] the chemistry of their amide analogues has not stimulated much interest so far. Thus, although the coupling of two different *trans*-β,γ-unsaturated-α-keto acids and a twofold excess of aniline using thionyl chloride was described,[8a] there is still a lack of a general, efficient and user friendly approach. In this field, palladium-catalyzed double carbonylation of alkenyl halides[20] nowadays leads the way. However, use of air-sensitive phosphine ligands and toxic carbon monoxide, under high-pressure and temperature conditions,[21] are major drawbacks of this reaction.

In accordance with our studies on the development of Michael addition-initiated domino multicomponent reactions,[22] we required a rapid, versatile and efficient methodology to prepare a variety of β,γ-unsaturated-α-keto amides. In this context, herein we wish to report a simple, metal-free, highly efficient and selective route to these valuable compounds (Scheme 1).



Scheme 1 General scheme for the coupling reaction

Indeed, we have now developed a peptidic coupling reaction involving stoichiometric amounts of easily available β,γ-unsaturated-α-keto acids[23] and amines. The reactions are performed in dichloromethane, at room temperature, in the presence of BOPCl and triethylamine, affording the desired products generally with excellent chemical purity. To initiate our study with a test reaction, we submitted a 1:1 mixture of (*E*)-2-oxo-4-phenylbut-3-enoic acid (**1a**)[23] and aniline (**2a**) to different peptidic coupling agents (Figure 1). The results are reported in Table 1.

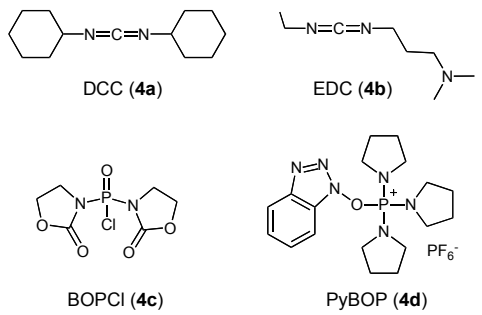
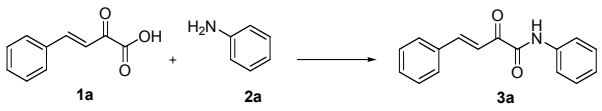


Figure 1 Various coupling agents.

Table 1: Screening of coupling systems for β,γ-unsaturated-α-keto amides formation.



entry	coupling system[a]	product	Yield (%)[b]
1	DCC (**4a**)/DMAP	mixture	-
2	EDC (**4b**)/HOBt	mixture	-
3	BOPCl (**4c**)/Et_3N	**3a**	99
4	PyBOP (**4d**)/DIPEA	**3a**	99

[a] for more experimental details, see ESI.
[b] Yields of crude product which needed no further purification.

Classical peptidic coupling systems such as DCC/DMAP[24] (entry 1) and EDC/HOBt[25] (entry 2) gave complex mixtures without significant traces of product (**3a**). In contrast, BOPCl (**4c**) combined with triethylamine[26] (entry 3) and PyBOP (**4d**) combined with diisopropylethylamine[27] (entry 4) were extremely efficient and afforded (**3a**) in quantitative yield and with excellent chemical purity.[28]

Stimulated by these results, we examined the scope of the protocol with several β,γ-unsaturated-α-keto acids and a variety of commercially available amines (Figure 2). BOPCl (**4c**), less expensive than PyBOP (**4d**), was elected as the coupling agent. The general applicability and efficiency of the reaction is clearly seen from the results depicted in Table 2. The reaction systematically afforded the expected *trans*-β,γ-unsaturated-α-keto amides in good to excellent yields, and with few exceptions, without need of further purification.

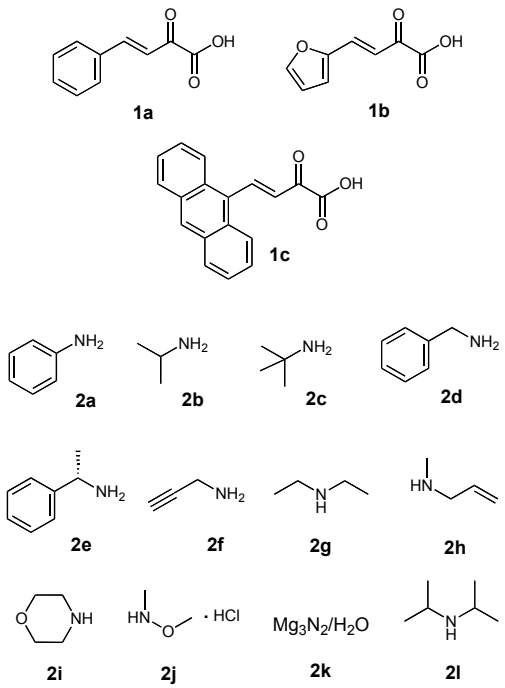


Figure 2 Substrates used in the study.

Aromatic amine such as aniline (**2a**) gave excellent results (entries 1, 11, 18), but reaction occurred also very well with aliphatic primary amines **2b-f** (entries 2-5, 12, 13). Additionally, secondary acyclic **2g**, **2h**, **2l** and cyclic amines **2i** were excellent substrates (entries 7-9, 14, 15, 19 and 20), affording an easy access to tertiary amides. Interestingly, amine hydrochloride salt can be used without previous neutralization as shown by the formation of α- keto Weinreb amides **3i** and **3p** (entries 9 and 16). Excess of triethylamine in the mixture is sufficient to reload *in situ* the Weinreb amine from **2j**, which can then perform peptidic coupling. Moreover, chiral amine **2e** was also easily introduced by the developed strategy (entry 13), allowing preparation of potential new Michael acceptors bearing a chiral inductor. Finally, this methodology provided a rapid synthetic access to challenging primary amides **3j** and **3q** using the system magnesium nitride/water **2k** as a source of ammonia[29] (entries 10 and 17). Multi-step sequences are generally required to prepare these substrates whereas they can be obtained in a single operation with this protocol.

In conclusion, we have developed a highly efficient route to *trans*-β,γ-unsaturated-α-keto amides from readily available β,γ-unsaturated-α-keto acids and various primary and secondary amines. Products are generally obtained in quantitative yield and with high chemical purity. This one-step method constitutes a good and general alternative to other previously published methodologies. We are currently developing the reactivity of these news products, especially as activated Michael acceptors in domino multicomponent processes.

Melting points (mp) were determined with a *Büchi Melting-point B-450* apparatus and were not corrected. ^{1}H and ^{13}C NMR spectra were recorded in solution respectively at 300.13 MHz and 75.47 MHz on a *Bruker AC 300* spectrometer. NMR data were collected at ambient temperature, and chemical shifts were given in ppm referenced to the appropriate solvent peak. Data for ^{1}H NMR are reported as follows: chemical shift, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quadruplet, , hept = heptuplet, dd = doublet of doublets, dt = doublet of triplets, dq = doublet of quadruplets, dhept = doublet of heptuplets, m = multiplet), integration. Low resolution mass spectra were recorded on a *Brucker Esquire 6000* with ESI source and high-resolution mass spectra were recorded on an API *QStar Elite* (Applied Biosystems SCIEX) mass spectrometer. Analytical thin layer chromatography was performed using *0.20 mm silica gel 60* plates. Flash chromatography was performed using *70-230 mesh silica gel 60* (Merck).

Synthesis of β-γ-unsaturated α-ketoacids 1; general procedure

To a solution of pyruvic acid (0.266 mol, 1 equiv), aromatic aldehyde (0.266 mol, 1 equiv) in methanol (15 mL) strirring in an ice bath, a solution of potassium hydroxide (0.398 mol, 1.5 equiv) in methanol (75 mL) was added. The first 50 mL of the base solution were added dropwise and the reaction temperature was kept below 25 °C. The ice bath was then removed and the rest of the base solution was added quickly. A yellow precipitate was formed at once. The solution was kept at ambient temperature for 1 h and then at 0 °C overnight. The yellow crystals were filtered off, washed twice with cold methanol and once with ether, and then dried to afford a potassium salt.[4] Water (300 mL) was added and then a 35% HCl solution was added dropwise under magnetic stirring until pH = 1. A precipitate was generally formed and ethyl acetate (300 mL) was added to the mixture. The layers were separated and the aqueous layer was extracted three times with ethyl acetate (150 mL). The organic layers were combined, washed with water (300 mL), brine (300 mL), and dried over sodium sulfate. After filtration on cotton, the solvent was removed under reduce pressure to afford β-γ-unsaturated-α-ketoacid **1** as a solid.

(*E*)-2-oxo-4-phenylbut-3-enoic acid 1a

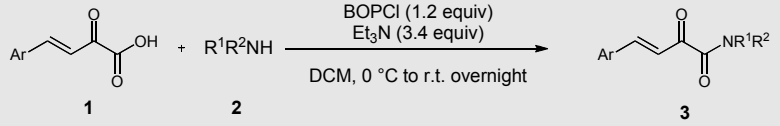
Yield: 49 %; yellow solid; mp = 58-59 °C.

MS (ESI) m/z (%): 199 $[M+Na]^+$ (100)

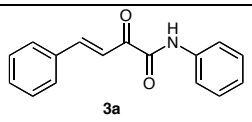
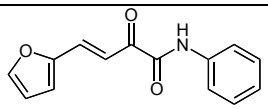
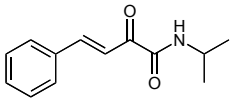
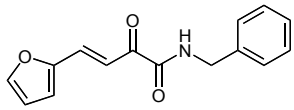
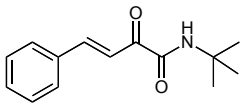
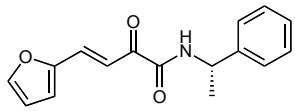
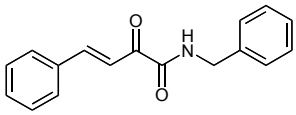
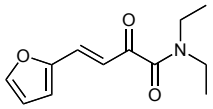
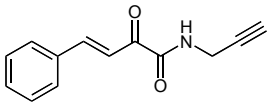
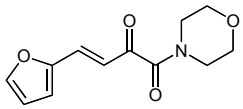
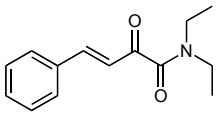
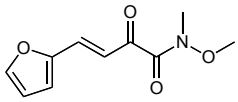
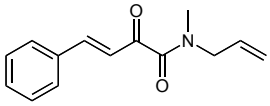
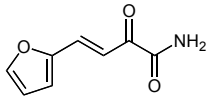
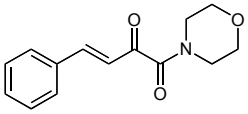
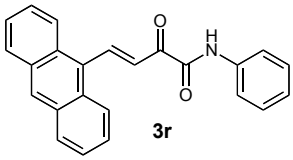
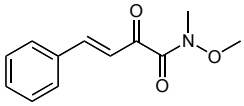
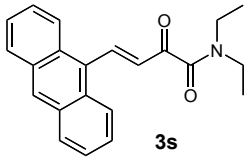
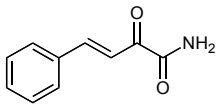
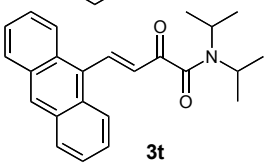
^{1}H NMR (300.13 MHz, $CDCl_3$): δ 7.40-7.49 (m, 3H), 7.58 (d, J = 15.9 Hz, 1H), 7.67 (d, J = 8.1 Hz, 2H), 8.11 (d, J = 15.6 Hz, 1H), 9.39 (br s, 1H).

^{13}C NMR (75.47 MHz, $CDCl_3$): δ 118.1, 129.2 (2C), 129.4 (2C), 132.3, 133.7, 151.0, 161.2, 182.7.

Table 2 Peptidic coupling of β,γ-unsaturated-α- keto acids with amines.



1 2 3

Entry	Acid 1	Amine 2	Product 3	Yield (%)[a]	Entry	Acid 1	Amine 2	Product 3	Yield (%)[a]
1	**1a**	**2a**	 **3a**	99	11	**1b**	**2a**	 **3k**	99
2	**1a**	**2b**	 **3b**	95	12	**1b**	**2d**	 **3l**	73[b]
3	**1a**	**2c**	 **3c**	98	13	**1b**	**2e**	 **3m**	75[b]
4	**1a**	**2d**	 **3d**	88	14	**1b**	**2g**	 **3n**	99
5	**1a**	**2f**	 **3e**	70	15	**1b**	**2i**	 **3o**	99
6	**1a**	**2g**	 **3f**	99	16	**1b**	**2j**	 **3p**	94
7	**1a**	**2h**	 **3g**	99	17	**1b**	**2k**	 **3q**	77
8	**1a**	**2i**	 **3h**	99	18	**1c**	**2a**	 **3r**	95
9	**1a**	**2j**	 **3i**	88	19	**1c**	**2g**	 **3s**	93
10	**1a**	**2k**	 **3j**	70	20	**1c**	**2l**	 **3t**	99

[a]yield of crude product which needed no further purifcation.
[b]Isolated yield after purification by flash chromatography over silica gel.

(*E*)-4-(furan-2-yl)-2-oxobut-3-enoic acid 1b

Yield: 67 %; brown solid; mp = 112-113 °C.

MS (ESI) m/z (%): 189 $[M+Na]^+$ (100).

^{1}H NMR (300.13 MHz, $CDCl_3$): δ 6.58 (dd, *J* = 3.4 Hz, *J* = 1.6 Hz, 1H), 6.93 (d, *J* = 3.6 Hz, 1H), 7.37 (d, *J* = 15.9 Hz, 1H), 7.62 (d, *J* = 1.2 Hz, $1H_8$), 7.88 (d, *J* = 15.9 Hz, 1H), 9.23 (br s, 1H). ^{13}C NMR (75.47 MHz, $CDCl_3$): δ 113.6, 115.4 ,120.2, 136.0, 147.3, 151.0, 160.7, 181.8.

(*E*)-4-(anthracen-10-yl)-2-oxobut-3-enoic acid 1c

Yield: 11 %; red solid; mp = 171-172 °C.

MS (ESI) m/z (%): 299 $[M+Na]^+$ (100).

HRMS (ESI) $[M+H]^+$: Calcd for $C_{18}H_{13}O_3^+$ 277.0859, found 277.0857.

^{1}H NMR (300.13 MHz, $CDCl_3$): δ 7.51-7.61 (m, 4H), 7.65 (d, *J* = 16.2 Hz, 1H) 8.05 (d, *J* = 8.1 Hz, 2H), 8.29 (d, *J* = 8.7 Hz, 2H), 8.54 (s, 1H), 9.26 (d, *J* = 16.2 Hz, 1H).

^{13}C NMR (75.47 MHz, $(CD_3)_2SO$): δ 124.6 (2C), 125.6 (2C), 127.0 (2C), 128.4, 128.8 (2C), 128.9 (2C), 129.0, 130.4, 130.7 (2C), 143.2, 163.9, 184.9.

Peptidic coupling of β-γ-unsaturated-α-ketoacids 1 with amines 2 using BOPCl; general procedure:

To a 10 mL one-necked round bottomed flask, equipped with a magnetic stirring bar and under argon atmosphere, were added β-γ-unsaturated-α-ketoacid **1** (200 mg, 1 equiv), freshly distilled dichloromethane (6 mL) and triethylamine (3.4 equiv). The solution was cooled at 0 °C and BOPCl **4c** (1.2 equiv) was added in a portion. The mixture was stirred at this temperature for 30 minutes, and the distilled amine **2** (1 equiv) was added. The reaction mixture was allowed to warm to room temperature and stirred overnight. Then it was diluted into dichloromethane (12 mL) and washed twice with an HCl 1N solution (30 mL), twice with water (30 mL) and once with brine (50 mL). The organic layer was dried on sodium sulfate, filtered on cotton and solvent was evaporated under reduce pressure to afford the corresponding β-γ-unsaturated-α-keto-amide **3** in excellent yield and very good chemical purity.

Particular cases: Primary amides **3j** and **3q** were formed by addition of magnesium nitride (1 equiv) instead of amine. The flask was sealed and water (6 equiv) was added to form ammonia *in situ*. The mixture was then stirred at room temperature overnight. For compounds **3i** and **3p**, hydrochloride form of Weinreb amine was used.

(*E*)-2-oxo-*N*-4-diphenylbut-3-enamide 3a

Yield: quant.; brown solid; mp = 140-141 °C.

MS (ESI) m/z (%): 274 $[M+Na]^+$ (100).

HRMS (ESI) $[M+H]^+$: Calcd for $C_{16}H_{14}NO_2^+$ 252.1019, found 252.1019.

^{1}H NMR (300.13 MHz, $CDCl_3$): δ 7.19 (t, *J* = 7.5 Hz, 1H), 7.37-7.46 (m, 5H), 7.70 (d, *J* = 7.5 Hz, 4H), 7.89 (d, *J* = 16.2 Hz, 1H), 8.03 (d, *J* = 15.9 Hz, 1H), 9.00 (br s, 1H).

^{13}C NMR (75.47 MHz, $CDCl_3$): δ 117.9, 119.8 (2C), 125.1, 129.0 (2C), 129.1 (2C), 129.2 (2C), 131.6, 134.2, 136.6, 148.7, 158.8, 185.4.

(*E*)-*N*-isopropyl-2-oxo-4-phenylbut-3-enamide 3b

Yield: 95%; yellow solid; mp = 66-67 °C.

TLC (AcOEt/petroleum ether: 1/6): R_f = 0.33.

MS (ESI) m/z (%): 240 $[M+Na]^+$ (100).

HRMS (ESI) $[M+H]^+$: Calcd for $C_{13}H_{16}NO_2^+$ 218.1176, found 218.1167.

^{1}H NMR (300.13 MHz, $CDCl_3$): δ 1.24 (d, *J* = 6.5 Hz, 6H), 4.11 (dhept, *J* = 8.3 Hz, *J* = 6.6 Hz, 1H), 7.03 (br s, 1H), 7.40-7.43 (m, 3H), 7.64-7.68 (m, 2H), 7.77 (d, *J* = 16.2 Hz, 1H), 7.93 (d, *J* = 16.2 Hz, 1H),.

^{13}C NMR (75.47 MHz, $CDCl_3$): δ 22.4 (2C), 41.6, 118.6, 129.0 (2C), 129.1 (2C), 131.3, 134.4, 147.8, 160.4, 185.7.

(*E*)-*N*-tert-butyl-2-oxo-4-phenylbut-3-enamide 3c

Yield: 98 %; yellow solid; mp = 90-91 °C.

MS (ESI) m/z (%): 254 $[M+Na]^+$ (100).

HRMS (ESI) $[M+H]^+$: Calcd for $C_{14}H_{18}NO_2^+$ 232.1332, found 232.1334.

^{1}H NMR (300.13 MHz, $CDCl_3$): δ 1.42 (s, 9H), 7.01 (br s, 1H), 7.36-7.39 (m, 3H), 7.61-7.64 (m, 2H), 7.79 (d, *J* = 16.2 Hz, 1H), 7.89 (d, *J* = 15.9 Hz, 1H).

^{13}C NMR (75.47 MHz, $CDCl_3$): δ 28.1 (3C), 51.1, 118.1, 128.8 (2C), 128.9 (2C), 131.1, 134.3, 147.3, 160.4, 186.1.

(*E*)-*N*-benzyl-2-oxo-4-phenylbut-3-enamide 3d

Yield: 88%; yellow solid; mp = 102-103 °C.

TLC (AcOEt/petroleum ether: 1/6): R_f = 0.28.

MS (ESI) m/z (%): 288 $[M+Na]^+$ (100).

HRMS (ESI) $[M+H]^+$: Calcd for $C_{17}H_{16}NO_2^+$ 266.1176, found 266.1176.

^{1}H NMR (300.13 MHz, $CDCl_3$): δ 4.55 (d, *J* = 6.1 Hz, 2H), 7.30-7.36 (m, 5H), 7.42-7.45 (m, 3H), 7.52 (br s, 1H), 7.66-7.69 (m, 2H), 7.80 (d, *J* = 16.1 Hz, 1H), 7.96 (d, *J* = 16.1 Hz, 1H).

^{13}C NMR (75.47 MHz, $CDCl_3$): δ 43.5, 118.6, 127.7, 127.8 (2C), 128.8 (2C), 129.0 (2C), 129.1 (2C), 131.5, 134.3, 137.1, 148.1, 161.1,185.3.

(*E*)-2-oxo-4-phenyl-*N*-(prop-2-ynyl)but-3-enamide 3e

Yield: 70%; orange gum.

TLC (AcOEt/petroleum ether: 1/4): R_f = 0.32.

MS (ESI) m/z (%): 236 $[M+Na]^+$ (100).

HRMS (ESI) $[M+H]^+$: Calcd for $C_{13}H_{12}NO_2^+$ 236.0682, found 236.0689.

^{1}H NMR (300.13 MHz, $CDCl_3$): δ 2.29 (t, *J* = 2.6 Hz, 1H), 4.15 (dd, *J* = 5.6 Hz, *J* = 2.6 Hz, 2H), 7.38-7.43 (m, 3H), 7.58 (br s, 1H), 7.65-7.68 (m, 2H), 7.74 (d, *J* = 16.2 Hz, 1H), 7.96 (d, *J* = 16.2 Hz, 1H).

^{13}C NMR (75.47 MHz, $CDCl_3$): δ 30.0, 73.1, 79.2, 119.2, 129.9 (2C), 130.0 (2C), 132.4, 135.1, 149.2, 161.7, 185.5.

(*E*)-*N*,*N*-diethyl-2-oxo-4-phenylbut-3-enamide 3f

Yield: quant.; brown oil.

MS (ESI) m/z (%): 254 $[M+Na]^+$ (100).

HRMS (ESI) $[M+H]^+$: Calcd for $C_{14}H_{18}NO_2^+$ 239.1332, found 239.1336.

^{1}H NMR (300.13 MHz, $CDCl_3$): δ 1.20 (t, *J* = 7.0 Hz, 3H), 1.24 (t, *J* = 7.0 Hz, 3H), 3.31 (q, *J* = 7.2 Hz, 2H), 3.51 (q, *J* = 7.2 Hz, 2H), 6.89 (d, *J* = 16.2 Hz, 1H), 7.40-7.43 (m, 3H), 7.55-7.58 (m, 2H), 7.61 (d, *J* = 16.2 Hz, 1H).

^{13}C NMR (75.47 MHz, $CDCl_3$): δ 12.7, 14.3, 39.1, 42.2, 123.6, 128.7 (2C), 129.0 (2C), 131.3, 134.0, 148.0, 166.6, 191.2.

(*E*)-*N*-allyl-*N*-methyl-2-oxo-4-phenylbut-3-enamide 3g

Yield: quant.; brown oil.

MS (ESI) m/z (%): 252 $[M+Na]^+$ (100).

HRMS (ESI) $[M+H]^+$: Calcd for $C_{14}H_{16}NO_2^+$ 230.1176, found 230.1176.

^{1}H NMR (300.13 MHz, $CDCl_3$): δ 2.88 (s, 3H), 2.93 (s, 3H), 3.81 (d, *J* = 5.7 Hz, 2H), 4.02 (d, *J* = 6.0 Hz, 2H), 5.12-5.22 (m, 4H), 5.64-5.81 (m, 2H), 6.84 (d, *J* = 16.2 Hz, 1H), 7.31-7.33 (m, 6H), 7.48-7.50 (m, 4H), 7.56 (d, *J* = 16.5 Hz, 1H), 7.57 (d, *J* = 16.2 Hz, 1H).

^{13}C NMR (75.47 MHz, $CDCl_3$): δ 31.6, 34.3, 48.7, 52.0, 118.1, 118.5, 123.0 (2C), 128.4 (4C), 128.7 (4C), 131.1 (2C), 131.2, 132.0, 133.5 (2C), 148.0, 148.1, 166.3, 166.8, 190.6, 190.8.

(*E*)-1-morpholino-4-phenylbut-3-ene-1,2-dione 3h

Yield: quant.; brown oil.

MS (ESI) m/z (%): 268 $[M+Na]^+$ (100).

HRMS (ESI) $[M+H]^+$: Calcd for $C_{14}H_{16}NO_3^+$ 246.1125, found 246.1123.

^{1}H NMR (300.13 MHz, $CDCl_3$): δ 3.39-3.42 (m, 2H), 3.59-3.62 (m, 2H), 3.65-3.70 (m, 4H), 6.87 (d, *J* = 16.5 Hz, 1H), 7.33-7.36 (m, 3H), 7.50-7.53 (m, 2H), 7.63 (d, *J* = 16.2 Hz, 1H),.

^{13}C NMR (75.47 MHz, $CDCl_3$): δ 41.5, 46.0, 66.3, 66.5, 123.0, 128.5 (2C), 128.8 (2C), 131.3, 133.5, 148.3, 165.0, 190.1.

(*E*)-*N*-methoxy-*N*-methyl-2-oxo-4-phenylbut-3-enamide 3i

Yield: 88%; scale up on 1 g of acid: quant.; orange oil.

MS (ESI) m/z (%): 242 $[M+Na]^+$ (100).

HRMS (ESI) $[M+H]^+$: Calcd for $C_{12}H_{14}NO_3^+$ 220.0968, found 220.0969.

^{1}H NMR (300.13 MHz, $CDCl_3$): δ 3.25 (s, 3H), 3.63 (s, 3H), 6.75 (d, *J* = 16.8 Hz, 1H), 7.33-7.36 (m, 3H), 7.49-7.52 (m, 2H), 7.51 (d, *J* = 16.5 Hz, 1H),.

^{13}C NMR (75.47 MHz, $CDCl_3$): δ 31.2, 61.9, 122.9, 128.4 (2C), 128.8 (2C), 131.1, 133.5, 148.1, 166.9, 190.6.

(E)-2-oxo-4-phenylbut-3-enamide 3j

Yield: 70%; brown solid; mp = 104-105 °C.

MS (ESI) m/z (%): 198 $[M+Na]^+$ (100), 176 $[M+H]^+$ (12).

HRMS (ESI) $[M+H]^+$: Calcd for $C_{10}H_{10}NO_2^+$ 176.0706, found 176.0699.

^{1}H NMR (300.13 MHz, $CDCl_3$): δ 6.39 (br s, 1H), 7.15 (br s, 1H), 7.39-7.41 (m, 3H), 7.62-7.65 (m, 2H), 7.71 (d, *J* = 16.2 Hz, 1H), 7.91 (d, *J* = 16.2 Hz, 1H).

^{13}C NMR (75.47 MHz, $CDCl_3$): δ 118.1, 128.9 (2C), 129.1 (2C), 131.5, 134.2, 148.1, 163.5, 185.0.

(*E*)-4-(furan-2-yl)-2-oxo-*N*-phenylbut-3-enamide 3k

Yield: quant.; brown solid; mp = 105-106 °C.

MS (ESI) m/z (%): 264 $[M+Na]^+$ (100).

HRMS (ESI) $[M+H]^+$: Calcd for $C_{14}H_{12}NO_3^+$ 242.0812, found 242.0812.

^{1}H NMR (300.13 MHz, $CDCl_3$): δ 6.56 (dd, *J* = 3.6 Hz, *J* = 1.7 Hz, 1H), 6.88 (d, *J* = 3.8 Hz, 1H), 7.16-7.20 (m, 1H), 7.39 (t, *J* = 7.9 Hz, 2H), 7.60 (d, *J* = 0.9 Hz, 1H), 7.67 (d, *J* = 1.5 Hz, 2H), 7.68 (d, *J* = 15.6 Hz, 1H), 7.80 (d, *J* = 15.9 Hz, 1H), 8.98 (br s, 1H).

^{13}C NMR (75.47 MHz, $CDCl_3$): δ 113.1, 115.7, 118.5, 119.7 (2C), 125.0, 129.1 (2C), 133.8, 136.6, 146.4, 151.4, 158.8, 185.1.

(*E*)-*N*-benzyl-4-(furan-2-yl)-2-oxobut-3-enamide 3l

Yield: 73%; orange solid; mp = 123-124 °C.

TLC (AcOEt/petroleum ether: 1/5): R_f = 0.34.

MS (ESI) m/z (%): 278 $[M+Na]^+$ (100).

HRMS (ESI) $[M+H]^+$: Calcd for $C_{15}H_{14}NO_3^+$ 256.0968, found 256.0964.

^{1}H NMR (300.13 MHz, $CDCl_3$): δ 4.53 (d, *J* = 6.3 Hz, 2H), 6.53 (dd, *J* = 1.8 Hz, *J* = 3.6 Hz, 1H), 6.82 (d, *J* =

3.3 Hz, 1H), 7.28-7.37 (m, 5H), 7.51 (br s, 1H), 7.57 (d, *J* = 1.8 Hz, 1H), 7.59 (d, *J* = 15.9 Hz, 1H), 7.73 (d, *J* = 15.9 Hz, 1H).

^{13}C NMR (75.47 MHz, $CDCl_3$): δ 43.4, 113.0, 116.5, 118.1, 127.7, 127.8 (2C), 128.7 (2C), 133.4, 137.1, 146.2, 151.5, 161.1, 185.1.

(*S*,*E*)-4-(furan-2-yl)-2-oxo-*N*-(1-phenylethyl)-but-3-enamide 3m

Yield: 75%; orange solid; mp = 86-87 °C.

TLC (AcOEt/petroleum ether: 1/5): R_f = 0.33.

MS (ESI) m/z (%): 292 $[M+Na]^+$ (100).

HRMS (ESI) $[M+H]^+$: Calcd for $C_{16}H_{16}NO_3^+$ 270.1125, found 270.1126.

^{1}H NMR (300.13 MHz, $CDCl_3$): δ 1.57 (d, *J* = 6.9 Hz, 3H),), 5.13 (dq, *J* = 8.4 Hz, *J* = 6.9 Hz, 1H), 6.51 (dd, *J* = 1.7 Hz, *J* = 3.5 Hz, 1H), 6.81 (d, *J* = 3.6 Hz, 1H), 7.27-7.30 (m, 1H), 7.34-7.35 (m, 4H), 7.47 (br s, 1H), 7.55 (d, *J* = 15.9 Hz, 1H), 7.56 (d, *J* = 1.5 Hz, 1H), 7.72 (d, *J* = 15.9 Hz, 1H).

^{13}C NMR (75.47 MHz, $CDCl_3$): δ 21.6, 49.0, 113.0, 116.5, 118.0, 126.1 (2C), 127.6, 128.7 (2C), 133.3, 142.2, 146.2, 151.5, 160.3, 185.2.

(*E*)-*N*,*N*-diethyl-4-(furan-2-yl)-2-oxobut-3-enamide 3n

Yield: quant.; brown oil.

MS (ESI) m/z (%): 244 $[M+Na]^+$ (100).

HRMS (ESI) $[M+H]^+$: Calcd for $C_{12}H_{16}NO_3^+$ 222.1125, found 222.1127.

^{1}H NMR (300.13 MHz, $CDCl_3$): δ 1.20 (t, *J* = 7.2 Hz, 3H), 1.23 (t, *J* = 7.2 Hz, 1H), 3.30 (q, *J* = 7.1 Hz, 2H), 3.49 (q, *J* = 7.2 Hz, 2H), 6.52 (dd, *J* = 3.5 Hz, *J* = 1.9 Hz, 1H), 6.75 (d, *J* = 3.6 Hz, 1H), 6.76 (d, *J* = 15.9 Hz, 1H), 7.37 (d, *J* = 15.9 Hz, 1H), 7.55 (d, *J* = 1.8 Hz, 1H).

^{13}C NMR (75.47 MHz, $CDCl_3$): δ 12.6, 14.2, 39.0, 42.0, 112.8, 117.4, 120.7, 133.3, 145.9, 150.5, 166.5,190.7.

(*E*)-4-(furan-2-yl)-1-morpholinobut-3-ene-1,2-dione 3o

Yield: quant.; brown oil.

MS (ESI) m/z (%): 258 $[M+Na]^+$ (100).

HRMS (ESI) $[M+H]^+$: Calcd for $C_{12}H_{14}NO_4^+$ 236.0917, found 236.0920.

^{1}H NMR (300.13 MHz, $CDCl_3$): δ 3.48-3.51 (m, 2H), 3.67-3.70 (m, 2H), 3.73-3.79 (m, 4H), 6.53 (dd, *J* = 3.4 Hz, *J* = 1.8 Hz, 1H), 6.79 (d, *J* = 3.6 Hz, 1H), 6.80 (d, *J* = 16.2 Hz, 1H), 7.43 (d, *J* = 15.9 Hz, 1H), 7.57 (d, *J* = 1.5 Hz, 1H).

^{13}C NMR (75.47 MHz, $CDCl_3$): δ 41.7, 46.2, 66.5, 66.7, 113.0, 117.9, 120.4, 133.7, 146.2, 150.5, 165.1, 189.7.

(*E*)-4-(furan-2-yl)-*N*-methoxy-*N*-methyl-2-oxobut-3-enamide 3p

Yield: 94%; brown oil.

MS (ESI) m/z (%): 210 $[M+H]^+$ (8), 232 $[M+Na]^+$ (100).

HRMS (ESI) $[M+H]^+$: Calcd for $C_{10}H_{12}NO_4^+$ 210.0761, found 210.0763.

^{1}H NMR (300.13 MHz, $CDCl_3$): δ 3.21 (s, 3H), 3.61 (s, 3H), 6.44 (dd, *J* = 1.5 Hz, *J* = 3.3 Hz, 1H), 6.57 (d, *J* = 16.5 Hz, 1H), 6.69 (d, *J* = 3.3 Hz, 1H), 7.23 (d, *J* = 16.5 Hz, 1H), 7.48 (d, *J* = 1.5 Hz, 1H).

^{13}C NMR (75.47 MHz, $CDCl_3$): δ 31.2, 61.9, 112.8, 117.5, 120.0, 133.5, 145.9, 150.2, 167.0, 190.0.

(*E*)-4-(furan-2-yl)-2-oxobut-3-enamide 3q

Yield: 77%; brown solid; mp = 97-98 °C.

MS (ESI) m/z (%): 188 $[M+Na]^+$ (100).

HRMS (ESI) $[M+H]^+$: Calcd for $C_8H_8NO_3^+$ 166.0499, found 166.0501.

^{1}H NMR (300.13 MHz, $CDCl_3$): δ 6.42 (br s, 1H), 6.51 (dd, *J* = 1.6 Hz, *J* = 3.5 Hz, 1H), 6.82 (d, *J* = 3.6 Hz, 1H), 7.16 (br s, 1H), 7.51 (d, *J* = 15.6 Hz, 1H), 7.55 (d, *J* = 1.5 Hz, 1H), 7.69 (d, *J* = 15.6 Hz, 1H).

^{13}C NMR (75.47 MHz, $CDCl_3$): δ 113.0, 116.0, 118.3, 133.5, 146.3, 151.3, 163.7, 184.7.

(*E*)-4-(anthracen-10-yl)-2-oxo-*N*-phenylbut-3-enamide 3r

Yield: 95%; orange solid; mp = 214-215 °C.

MS (ESI) m/z (%): 374 $[M+Na]^+$ (100).

HRMS (ESI) $[M+H]^+$: Calcd for $C_{24}H_{18}NO_2^+$ 352.4052, found 352.4049.

^{1}H NMR (300.13 MHz, $CDCl_3$): δ 7.21 (t, *J* = 7.4 Hz, 1H), 7.42 (t, *J* = 7.9 Hz, 2H), 7.46-7.59 (m, 4H), 7.75 (d, *J* = 9.6 Hz, 2H), 7.92 (d, *J* = 16.2 Hz, 1H), 8.03 (d, *J* = 9.3 Hz, 2H), 8.32 (d, *J* = 8.7 Hz, 2H), 8.50 (s, 1H), 9.10 (br s, 1H), 9.11 (d, *J* = 16.2 Hz, 1H).

^{13}C NMR (75.47 MHz, $CDCl_3$): δ 119.8 (2C), 124.9 (2C), 125.2, 125.5 (2C), 126.8, 127.0 (2C), 128.8 (2C), 129.0 (2C), 129.2 (2C), 129.8 (2C), 129.9, 131.2, 136.5, 145.9, 158.8, 185.1.

(*E*)-4-(anthracen-10-yl)-*N*,*N*-diethyl-2-oxobut-3-enamide 3s

Yield: 93%; brown oil.

MS (ESI) m/z (%): 354 $[M+Na]^+$ (100).

HRMS (ESI) $[M+H]^+$: Calcd for $C_{22}H_{22}NO_2^+$ 332.1645, found 332.1645.

^{1}H NMR (300.13 MHz, $CDCl_3$): δ 0.31 (t, *J* = 7.2 Hz, 3H), 0.79 (t, *J* = 7.1 Hz, 3H), 1.30 (t, *J* = 7.1 Hz, 3H), 1.32 (t, *J* = 7.1 Hz, 3H), 2.38 (q, *J* = 7.1 Hz, 2H), 2.66 (q, *J* = 7.1 Hz, 2H), 3.48 (q, *J* = 7.3 Hz, 2H), 3.58 (q, *J* = 7.8 Hz, 2H), 6.91 (d, *J* = 16.8 Hz, 1H), 7.02 (d, *J* = 12.0

Hz, 1H), 7.43-7.55 (m, 8H), 7.87 (d, J = 12.3 Hz, 1H), 7.95-8.05 (m, 6H), 8.21 (d, J = 8.7 Hz, 2H), 8.40 (d, J = 9.0 Hz, 2H), 8.64 (d, J = 16.5 Hz, 1H).

^{13}C NMR (75.47 MHz, $CDCl_3$): δ 11.6, 12.8, 13.5, 14.4, 38.5, 38.5, 39.2, 41.3, 42.3, 124.6 (2C), 125.3 (2C), 125.4 (2C), 125.6 (2C), 125.9 (2C), 126.8 (2C), 127.5, 128.2 (2C), 128.5 (2C), 128.8 (2C), 128.9 (2C), 129.3 (4C), 129.3, 130.9, 131.0, 131.7, 132.1, 142.0, 145.4, 165.2, 166.5, 189.9, 190.9.

(*E*)-4-(anthracen-9-yl)-*N*,*N*-diisopropyl-2-oxobut-3-enamide 3t

Yield: quant.; brown oil.

MS (ESI) m/z (%): 360 $[M+H]^+$ (8), 382 $[M+Na]^+$ (100).

HRMS (ESI) $[M+H]^+$: Calcd for $C_{24}H_{26}NO_2^+$ 360.1958, found 360.1961.

^{1}H NMR (300.13 MHz, $CDCl_3$): δ 1.33 (d, J = 6.6 Hz, 6H), 1.60 (d, J = 6.6 Hz, 6H), 3.63 (hept., J = 6.7 Hz, 1H), 4.03 (hept., J = 6.6 Hz, 1H), 6.81 (d, J = 16.8 Hz, 1H), 7.46-7.55 (m, 4H), 8.00 (d, J = 7.5 Hz, 2H), 8.20 (d, J = 9.0 Hz, 2H), 8.44 (s, 1H), 8.61 (d, J = 16.5 Hz, 1H).

^{13}C NMR (75.47 MHz, $CDCl_3$): δ 20.2, 20.7, 46.0, 50.2, 124.6, 125.3 (2C), 125.4 (2C), 126.8 (2C), 128.9 (3C), 129.2 (2C), 131.1 (2C), 132.4, 145.5, 166.9, 191.2.

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